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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Susan Acton, *et al.*

Serial No.: 09/779,152

Filed: February 8, 2001

For: *DIAGNOSTIC ASSAYS AND KITS FOR BODY MASS AND CARDIOVASCULAR DISORDERS*

Attorney Docket No.: MNI-172CP2

Group Art Unit: 1634

Examiner: Chakrabarti, A.

Commissioner for Patents
Washington, D.C. 20231

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June 17, 2002
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AMENDMENT AND RESPONSE

Dear Sir:

This communication is in response to the Office Action dated March 15, 2002 (Paper No. 10). Please amend the above-identified application as follows:

In the claims:

Please amend claims 1-20 and 22 as follows:

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1. **(Amended)** A method for determining whether a subject has, or is at risk of developing, an abnormally low HDL level, comprising determining the identity of the allelic

variant of a polymorphic region of the SR BI gene of the subject and comparing the allelic variant of the subject with allelic variants associated with abnormally low HDL levels, to thereby determine whether the subject has an allelic variant of a polymorphic region of an SR-BI gene associated with an abnormally low HDL level.

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2. **(Amended)** The method of claim 1, wherein the polymorphic region is located in an exon.

3. **(Amended)** The method of claim 2, wherein the exon is exon 8.

4. **(Amended)** The method of claim 3, wherein the polymorphic region is a nucleotide polymorphism.

5. **(Amended)** The method of claim 4, wherein the nucleotide polymorphism is located at position 41 of exon 8.

6. **(Amended)** The method of claim 5, wherein nucleotide 41 of exon 8 of the SR-BI gene in a normal subject is a thymidine and the presence of a nucleotide other than a thymidine at position 41 of exon 8 in the SR-BI gene of a subject indicates that the subject has or is at risk of developing an abnormally low HDL level.

7. **(Amended)** The method of claim 6, wherein the nucleotide other than a thymidine at position 41 of exon 8 is a cytidine.

8. **(Amended)** The method of claim 1, wherein determining the identity of the allelic variant of a polymorphic region of an SR-BI gene comprises determining the identity of at least one nucleotide of the polymorphic region.

9. **(Amended)** The method of claim 2, wherein determining the identity of the allelic variant of a polymorphic region comprises contacting a nucleic acid of the subject with at least one probe or primer which is capable of hybridizing to an SR-BI gene.

10. **(Amended)** The method of claim 9, wherein the probe or primer is capable of specifically hybridizing to an allelic variant of the polymorphic region.

11. **(Amended)** The method of claim 10, wherein the probe or primer is capable of specifically hybridizing to an allelic variant having a thymidine at position 41 of exon 8 of the SR-BI gene.

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12. **(Amended)** The method of claim 1, wherein the probe or primer has a nucleotide sequence from about 15 to about 30 nucleotides.

13. **(Amended)** The method of claim 1, wherein the probe or primer is a single stranded nucleic acid.

14. **(Amended)** The method of claim 1, wherein the probe or primer is labeled.

15. **(Amended)** The method of claim 1, wherein determining the identity of the allelic variant of a polymorphic region is carried out by allele specific hybridization.

16. **(Amended)** The method of claim 1, wherein determining the identity of the allelic variant of a polymorphic region is carried out by primer specific extension.

17. **(Amended)** The method of claim 1, wherein determining the identity of the allelic variant of a polymorphic region is carried out by an oligonucleotide ligation assay.

18. **(Amended)** The method of claim 1, wherein determining the identity of the allelic variant of a polymorphic region comprises performing a restriction enzyme site analysis.

19. **(Amended)** The method of claim 18, wherein the restriction enzyme is a HaeIII enzyme.

20. **(Amended)** The method of claim 1, wherein determining the identity of the allelic variant of a polymorphic region is carried out by single-stranded conformation polymorphism.

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22. **(Amended)** The method of claim 21, comprising determining the identity of the nucleotide at position 41 in exon 8 and/or nucleotide 54 in intron 5, wherein the presence of a cytidine at position 41 of exon 8 and/or the presence of a thymidine at position 54 of intron 5 indicates that the subject has or is at risk of developing an abnormally low HDL level.

REMARKS

Claims 1-22 and 35-38 are currently pending in this application. Claims 1-20 and 22 have been amended. Accordingly, claims 1-22 and 35-38 will remain pending in the instant application upon entry of the instant claim amendments.

Attached hereto is Appendix A titled "**Version with Markings to Show Changes Made**," which indicates the specific amendments made to the specification and the claims. For the Examiner's convenience, a copy of the claims that will be pending upon entry of the amendments presented herein is attached hereto as Appendix B.

Amendment of the claims should in no way be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or one or more separate applications.

Applicants request that the amendments to the claims be entered into the record of this application.

Double Patenting

Claims 1-22 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-11, and 30-51 of U.S. Patent No. 6,228,581 B1 (May 8, 2001). In particular, the Examiner is of the opinion that

> Although the conflicting claims are not identical, they are not patentably distinct from each other because U.S. Patent 6,228,581 Bl clearly teaches a method for determining whether a male subject has, or is at risk of developing, an abnormally low HDL level. The male subject species as claimed in U.S. Patent 6,228,581 B1 anticipates the genus subject of the instant claimed invention. Moreover, the SR-Bl gene that is associated with high HDL level as claimed in U.S. Patent 6,228,581 Bl obviously and automatically indicates the status of the SR-B1 gene that is associated with low HDL level.

While in no way admitting that claims 1-22 are obvious over claims 10-11 and 30-51 of U.S. Patent No. 6,228,581 B1, upon allowance of the present application, Applicants will consider submitting a terminal disclaimer in compliance with 37 C.F.R. 1.321(b) and (c), if appropriate, which will obviate this rejection.

Claim Rejections

Rejection of Claims 1-22 and 34-38 Under 35 U.S.C. §112, First Paragraph-Enablement

The Examiner has rejected claims 1-22 and 34-38 under 35 U.S.C. §112, first paragraph because "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." In particular, with respect to claims 1-22, the Examiner states that

> the claim is broadly drawn to method of determining risk of developing an abnormally low HDL level in any subject associated with the polymorphic region of the SR-BI gene and the method of predicting the effect of hormone replacement therapy on the HDL level in a female subject associated with the allelic variants of the SR-BI gene. ***However, the specification does not provide guidance commensurate in scope with this claim, teaching no example of any association of HDL level in female allelic variants of SR-BI gene.*** The specification provides minimal guidance regarding methods for the identification of alternate methodology of any risk factor (abnormal HDL levels) in any subjects of any animal species (including human) associated with the presence of allelic variant of SR-BI gene other than haplotypes 111, 112, 121, 211, 212, and 221 of three human populations named as ASHKENAZI, FINNISH, and SEDISH. (Emphasis added).

With respect to claims 34-38, the Examiner is of the opinion that

> There is no working example of any hormone treatment or drug trial and its efficacy in any patients of any animal species (including human) associated with the presence of allelic variant of SR-B I gene. It is highly unpredictable whether or what other treatments would function in the context of highly variant alleles of SR-BI genes in different human population and different animal species. It is therefore highly unpredictable whether other diagnostic strategies can be identified which meets this specific criteria regarding the method of determining risk of developing an abnormally low HDL level in any subject associated with the polymorphic region of the SR-BI gene and the method of predicting the effect of hormone replacement therapy on the HDL level in a female subject associated with the allelic variants of the SR-BI gene. Further, hormone treatment regiment will be by the trial and error method. This trial and error requirement is borne out because effects of hormone therapy on any disease in any patients of any animal species (including human) associated with the presence of polymorphism cannot be readily deduced, even where the metabolic pathways are known. Further, each disease in any patients of any animal species (including human) associated with the presence of polymorphism has unpredictable effects on metabolic function, and no

> general method for a priori selection of diagnosis and hormone treatment is presented.

Applicants respectfully traverse and request reconsideration. The present invention features several polymorphic regions in the SR-B1 gene that are associated with specific diseases or disorders, including abnormal body mass and abnormal lipoprotein levels, *i.e.*, low HDL levels, in both females and males. In particular, as taught in the instant specification, a female or a male subject with the more common allele (cytidine) at residue 41 of exon 8 of SR-BI (EX8C) has or is likely to have a tendency of having or developing lower HDL levels than a female or a male subject having the less common allele (thymidine) at that position (EX8T). A female subject with the less common allele (thymidine) at residue 54 of intron 5 (IVS5T) has or is likely to have or develop low HDL levels, relative to a female subject having the more common allele (cytidine) at that position (IVS5C); a female subject having both EX8C and IVS5T has greater than four-fold increased odds of having or developing low HDL levels as compared to a female subject having EX8T and IVS5C (see *e.g.*, page 7, line 26 through page 8, line 6 of the instant specification). Contrary to the Examiner's statement that the specification contains "no example of any association of HDL level in female allelic variants of SR-Bl gene," Applicants respectfully submit that the instant specification at, for example, page 15, lines 21-35, Table III, and Example 6, clearly describes the association of low HDL level with SR-B1 polymorphisms in females and in males. The replication of these results in multiple, ethnically diverse populations adds considerable validity to these results.

Furthermore, the instant application teaches that associations between SR-B1 polymorphisms and low HDL are influenced by gender, and that SR-B1 polymorphisms are useful in predicting the effect of hormone replacement therapy (HRT) on HDL levels in female subjects, *e.g.*, postmenopausal female subjects. In particular, the specification teaches that SR-B1 variants modulate the effect of HRT on HDL levels in women. For example, a postmenopausal woman may have the EX8C and IVS5T variants, but may have normal HDL. However, treatment with HRT may cause low HDL. Therefore, in females, the identification of SR-B1 variants (*e.g.*, EX8C and/or IVS5T) may be used to predict the effect HRT would have on HDL level (*e.g.*, lowering HDL level) (see *e.g.*, page 16, lines 8-16). Furthermore, as taught at page 15, line 36 through page 16, line 7 of the instant specification:

> [i]t is well known that HDL levels are affected by sex hormone status. Furthermore, the expression of SR-B1 is known to be regulated by estrogen. Estrogen treatment of rats has been shown to downregulate SR-B1 in the liver (Fluiter K, et al. (1998) *J Biol Chem.* 273:8434-8). Moreover, overexpression of SR-B1 in the liver has been demonstrated to result in a pronounced fall in plasma HDL (Kozarsky KF (1997) *Nature* 387:414-7).

> It is possible that the downregulation of SR-B1 by estrogen is impaired by a genetic variant in SR-B1, resulting in an increased expression of SR-B1 and therefore lower HDL levels in women. This same effect may not be apparent in men as estrogen does not play as key a role in the modulation of HDL.

The invention further provides materials and methods such as nucleic acids, (*e.g.* intronic sequences, useful as probes or primers) for determining the identity of other allelic variants of an SR-B1 polymorphic region as well as materials and methods for determining the identity of the alleles of a specific polymorphic region of an SR-B1 gene (see *e.g.*, Examples 1-4 of the instant specification). Such methods can be used, for example, to determine whether a subject has or is at risk of developing a disease or condition associated with one or more specific alleles of polymorphic regions of an SR-B1 gene (see *e.g.*, Example 5 of the instant specification).

Applicants thus submit that once provided with the teachings and guidelines of the present invention as disclosed in the specification, the procedures for carrying out the claimed invention become routine to one skilled in the art. As stated by the Board, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex Parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. Applicants submit that they have provided more than ample support for the presently claimed methods to enable one skilled in the art to practice the claimed invention. Applicants therefore request withdrawal of the §112, first paragraph, enablement rejection of claims 1-22 and 34-38.

Rejection of Claims 1-22 and 34-38 Under 35 U.S.C. §112, First Paragraph-Written Description

The Examiner has rejected claims 1-22 and 34-38 under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> The specification discloses only six haplotypes which corresponds to the cDNA/genomic DNA encoding the human species associated with the LDL or HDL polymorphism. Claims 1-22, and 34-38 are directed to encompass all gene sequences, sequences that are polymorphic region of the SR-BI gene corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. ***Moreover, only association of HDL levels with the allelic variant has been demonstrated in man (Figure 7 and page 87, lines 17-19 of the specification). However, no association of HDL level in female allelic variants of SR-B1 gene has been disclosed (Figure 6) in the specification.*** The specification provides insufficient written description to support the genus encompassed by the claim....With the exception of haplotypes 111, 112, 121,211,212, and 221, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. (Emphasis added).

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that the specification provides more than adequate written description to support the claimed invention.

In order to meet the written description requirement of the first paragraph of 35 U.S.C. § 112, it is not necessary that a patent specification describe each and every specific member of a genus recited in a claim.

The sufficiency of a disclosure in meeting the written description requirement of 35 U.S.C. §112 for claims to a genus of cDNAs was addressed in *The Regents of the University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), in which the Federal Circuit stated:

> [a] description of a genus of cDNAs may be achieved by means of a recitation of ***a representative number of cDNAs, defined by nucleotide sequence,*** falling within the scope of the genus or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus [*emphasis added*].

Therefore, a claim to a genus of chemical compounds satisfies the written description requirement when its accompanying specification defines by sequence a representative number

of its members falling within the scope of the genus. For reasons discussed in detail below, the instant specification satisfies this requirement for the claimed invention.

The instant specification describes several polymorphic regions of the SR-B1 which are associated with HDL levels in both females and males (see, *e.g.*, page 4, line 12 through page 6, line 3 of the instant specification). Furthermore, haplotype analysis was carried out with the three most common polymorphisms (see, *e.g.*, page 87 of the instant specification).

Moreover, as set forth above and contrary to the Examiner's statement that "no association of HDL level in female allelic variants of SR-B1 gene has been disclosed (Figure 6) in the specification," Applicants respectfully submit that the instant specification at, for example, page 15, lines 21-35, Table III, and Example 6 clearly describes the association of low HDL level with SR-B1 polymorphisms in females and in males.

In summary, Applicants have described a genus of allelic variants which are defined by nucleic acid sequence and are related based on their association to HDL and/or LDL levels. Thus, the instant specification satisfies the written description requirement for the claimed invention.

Applicants submit that one skilled in the art would recognize that the inventor, at the time the application was filed, had possession of the claimed invention, and therefore respectfully requests reconsideration and withdrawal of the foregoing rejection.

Rejection of claims 2-20 and 22 under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected claims 2-20 and 22 under 35 U.S.C. §112, second paragraph as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[c]laims 2-20, and 22 recite the limitation "A" in the beginning of each claim. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully traverse. However, in the interest of expediting prosecution and in no way conceding to the validity of the Examiner's position, claims 2-20 and 22 have been amended to such that "A" is no longer recited at the beginning of each claim, thereby obviating the foregoing rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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